Reply to the comment of Wilbrink et al. on Retrospective analysis of liraglutide and basal insulin combination therapy in Japanese type 2 diabetes: The association between remaining β-cell function and the achievement of the HbA1c target 1 year ...

AUTHOR(S):

Usui, Ryota; Sakuramachi, Yui; Seino, Yusuke; Murotani, Kenta; Kuwata, Hitoshi; Tatsuoka, Hisato; Hamamoto, Yoshiyuki; Kurose, Takeshi; Seino, Yutaka; Yabe, Daisuke

京都大学 KYOTO UNIVERSITY
JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
京都大学学術情報リポジトリ KURENAI 紅 Kyoto University Research Information Repository
LETTER TO THE EDITOR

Reply to the comment of Wilbrink *et al.* on Retrospective analysis of liraglutide and basal insulin combination therapy in Japanese type 2 diabetes: The association between remaining β-cell function and the achievement of the HbA1c target 1 year after initiation

We would like to thank Wilbrink *et al.*[1] for their interest and comments on our recent article regarding the glycated hemoglobin (HbA1c)-lowering effect of glucagon-like peptide-1 receptor agonist liraglutide with basal insulin among Japanese individuals with type 2 diabetes.

We have reported that the HbA1c-lowering effects of liraglutide/basal insulin combination rely on remaining β-cell function, and that the cut-off value of the C-peptide immunoreactivity index, a β-cell function-related index frequently used in Japanese clinical settings, is 1.103 for the achievement of HbA1c < 7.0% at 54 weeks after initiating the liraglutide/basal insulin combination[2]. In our study, we found that changes in HbA1c were not affected by type 2 diabetes duration, unlike the Wilbrink *et al.* study (Figure 1b). This discrepancy might be due to several reasons. First, we studied patients receiving liraglutide/basal insulin combination in replacement of multiple daily injection insulin therapy or basal insulin-supported oral therapy, whereas Wilbrink *et al.* studied those receiving liraglutide in replacement of insulin therapy. We previously showed that discontinuation of liraglutide as a result of hyperglycemia after switching from insulin is affected by remaining β-cell function and type 2 diabetes duration[3]. In addition, we also reported that the HbA1c-lowering effects of liraglutide monotherapy and sulfonylurea combination rely on remaining β-cell function and type 2 diabetes duration (Figure 1a) in a study in which 74% of the study patients had been taking insulin before initiating liraglutide[4]. Importantly, the C-peptide immunoreactivity index cut-off value for HbA1c < 7.0% achievement by liraglutide monotherapy and sulfonylurea combination was higher than that of liraglutide/basal combination (1.86 and 1.10, respectively)[2,4]. It is widely accepted that β-cell function progressively declines over time in type 2 diabetes patients, making it difficult to obtain appropriate glycemic control without insulin use[5,6]. It is possible that basal insulin co-administration compensated for the decline in β-cell function associated with longer type 2 diabetes duration in our study[2]. Indeed, it was shown that the addition of basal insulin significantly improved HbA1c in individuals inadequately controlled by liraglutide[7]. Second, the discrepancy between our study and the Wilbrink *et al.* study might be due to ethnic difference in type 2 diabetes pathophysiology. Type 2 diabetes in East Asian patients is characterized primarily by non-obesity and β-cell dysfunction, unlike type 2 diabetes in Caucasian patients, which is characterized by obesity and insulin resistance[8]. As impaired β-cell function is observed even in the early stage of type 2 diabetes in East Asian patients, type 2 diabetes duration might have less significance in predicting the HbA1c-lowering effects of liraglutide. Third, the discrepancy might be due to limited sample size (the Usui study on liraglutide/basal insulin, $n = 38$; the Usui study on liraglutide monotherapy or sulfonylurea combination, $n = 88$; and the Wilbrink *et al.* study, $n = 69$). Dependence of HbA1c-lowering effects of liraglutide/basal insulin combination on type 2 diabetes duration awaits further investigation by studies with larger sample sizes. Nevertheless, it is conceivable that liraglutide exerts greater HbA1c-lowering effects in the early stage of type 2 diabetes when ample β-cell function remains, and that addition of basal insulin or other antidiabetic drugs is required when β-cell function becomes substantially reduced.

*Corresponding author. Daisuke Yabe
Tel.: +81-78-303-6090
Fax: +81-78-303-6090
E-mail address: ydaisuke-kyoto@umin.ac.jp
Present address: †Department of Diabetes, Endocrinology and Nutrition, Graduate School of Medicine, Kyoto University, 54 Shogo-in, Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan.
‡Department of Endocrinology Tenri Hospital Tenri, Nara 632-8552, Japan.
§These authors contributed equally to the study.
Received 23 April 2018; accepted 24 April 2018

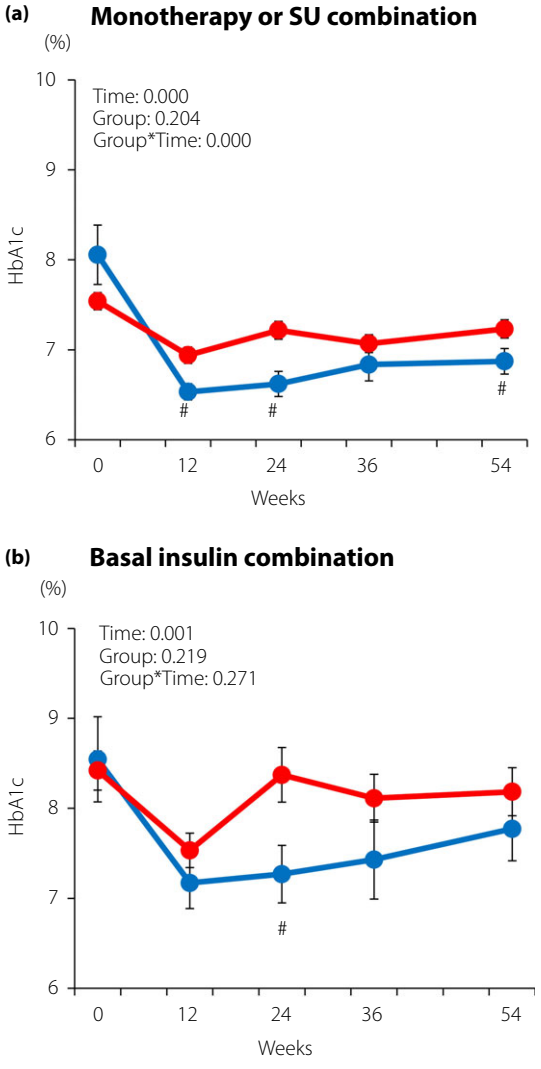

Figure 1 | Changes of glycated hemoglobin (HbA1c) in Japanese patients with type 2 diabetes receiving (a) liraglutide monotherapy or sulfonylureas (SU) combination and (b) liraglutide/basal insulin combination. The patients were subdivided into two groups by medians of type 2 diabetes duration: (a) 10 years and (b) 16 years. Blue, those with type 2 diabetes duration below the median: (a) $n = 37$ and (b) $n = 18$); and red, those with type 2 diabetes duration with the median or above: (a) $n = 51$ and (b) $n = 19$). Time-course curves were analyzed by mixed-effects models including group, time, and the interaction of group and time, and the *P*-values are shown. $^{\#}P < 0.05$ (*vs* patients with the median or above) by the Mann–Whitney *U*-test. The statistical analysis was carried out using SPSS Statistics 24 software (IBM Corp., Armonk, New York, USA). Each value represents the mean ± standard error of the mean.

DISCLOSURE

Daisuke Yabe received consulting or speaker fees from MSD K.K., Novo Nordisk Pharma Ltd., Takeda Pharmaceutical Company Limited and Taisho Toyama Pharmaceutical Co. Ltd. Daisuke Yabe also received clinically commissioned/joint research grants from Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly and Company, Taisho Toyama Pharmaceutical Co. Ltd., MSD K.K., Ono Pharmaceutical Co. Ltd., Novo Nordisk Pharma Ltd., Arklay Co. Ltd., and Takeda Pharmaceutical Company Limited. Yoshiyuki Hamamoto received consulting or speaker fees from Novo Nordisk Pharma Ltd. Takeshi Kurose received consulting or speaker fees from Sanofi K.K. Takeshi Kurose also received clinically commissioned/joint research grants from the Japan Vascular Disease Research Foundation. Yutaka Seino received consulting or speaker fees from Eli Lilly Japan K.K., Sanofi K.K., Novo Nordisk Pharma Inc., Glaxo-Smith-Kline, Taisho Pharmaceutical Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Astellas Pharma Inc., BD, Nippon Boehringer Ingelheim Co., Ltd., Johnson & Johnson and Takeda Pharmaceutical Company Limited. Yutaka Seino also received clinically commissioned/joint research grants from Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly and Company, Taisho Toyama Pharmaceutical Co. Ltd., MSD K.K., Ono Pharmaceutical Co. Ltd., Novo Nordisk Pharma Ltd., and Arklay Co. Ltd. R. The other authors declare no conflict of interest.

Ryota Usui[1,§,†], Yui Sakuramachi[1,2,§,‡], Yusuke Seino[3], Kenta Murotani[4], Hitoshi Kuwata[1,2], Hisato Tatsuoka[1,2], Yoshiyuki Hamamoto[1,2,5], Takeshi Kurose[1,2], Yutaka Seino[1,2], Daisuke Yabe[1,2,6,7]*

[1]*Center for Diabetes, Endocrinology and Metabolism, Kansai Electric Power Hospital, Osaka,* [2]*Yutaka Seino Distinguished Center for Diabetes Research, Kansai Electric Power Medical Research Institute, Kobe,* [3]*Department of Endocrinology and Diabetes Metabolic Medicine, Nagoya University Graduate School of Medicine, Nagoya,* [4]*Division of Biostatistics, Clinical Research Center, Aichi Medical University Hospital, Nagakute,* [5]*Center for Metabolism and Clinical Nutrition, Kansai Electric Power Hospital, Osaka,* [6]*Division of Molecular and Metabolic Medicine, Department of Physiology and Cell Biology, Kobe University Graduate School of Medicine, Kobe,* [7]*Department of Diabetes, Endocrinology and Nutrition, Kyoto University Graduate School of Medicine, Kyoto, Japan*

REFERENCES

1. Wilbrink FJ, Mudde AH, Mulder AH, *et al.* Disease duration as an indicator of the efficacy of liraglutide in patients

with type 2 diabetes mellitus. *J Diabet Investig* 2018. https://doi.org/10.1111/jdi.12857
2. Usui R, Sakuramachi Y, Seino Y, *et al*. Retrospective analysis of liraglutide and basal insulin combination therapy in Japanese type 2 diabetes patients: the association between remaining β-cell function and the achievement of the glycated hemoglobin target 1 year after initiation. *J Diabetes Investig* 2017. https://doi.org/10.1111/jdi.12773
3. Usui R, Yabe D, Kuwata H, *et al*. Retrospective analysis of safety and efficacy of insulin-to-liraglutide switch in Japanese type 2 diabetes: a caution against inappropriate use in patients with reduced beta-cell function. *J Diabetes Investig* 2013; 4: 585–594.
4. Usui R, Yabe D, Kuwata H, *et al*. Retrospective analysis of safety and efficacy of liraglutide monotherapy and sulfonylurea-combination therapy in Japanese type 2 diabetes: association of remaining beta-cell function and achievement of HbA1c target one year after initiation. *J Diabetes Complications* 2015; 29: 1203–1210.
5. Yagihashi S, Inaba W, Mizukami H. Dynamic pathology of islet endocrine cells in type 2 diabetes: beta-Cell growth, death, regeneration and their clinical implications. *J Diabetes Investig* 2016; 7: 155–165.
6. Funakoshi S, Fujimoto S, Hamasaki A, *et al*. Analysis of factors influencing pancreatic β-cell function in Japanese patients with type 2 diabetes: association with body mass index and duration of diabetic exposure. *Diabetes Res Clin Pract* 2008; 82: 353–358.
7. Rosenstock J, Rodbard HW, Bain SC, *et al*. One-year sustained glycemic control and weight reduction in type 2 diabetes after addition of liraglutide to metformin followed by insulin detemir according to HbA1c target. *J Diabetes Complications* 2013; 27: 492–500.
8. Yabe D, Seino Y. Type 2 diabetes via beta-cell dysfunction in east Asian people. *Lancet Diabetes Endocrinol* 2016; 4: 2–3.

Doi: 10.1111/jdi.12858